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Relative rates of cancers and deaths in Australian communities with PFAS environmental contamination associated with firefighting foams: A cohort study using linked data

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ABSTRACT

Background: Per- and polyfluoroalkyl substances (PFAS) are environmental contaminants that are potentially harmful to health. We examined if rates of selected cancers and causes of deaths were elevated in three Australian communities with local environmental contamination caused by firefighting foams containing PFAS. The affected Australian communities were Katherine in Northern Territory, Oakey in Queensland and Williamtown in New South Wales.

Methods: All residents identified in the Medicare Enrolment File (1983–2019)—a consumer directory for Australia's universal healthcare—who ever lived in an exposure area (Katherine, Oakey and Williamtown), and a sample of those who ever lived in selected comparison areas, were linked to the Australian Cancer Database (1982–2017) and National Death Index (1980–2019). We estimated standardised incidence ratios (SIRs) for 23 cancer outcomes, four causes of death and three control outcomes, adjusting for sex, age and calendar time of diagnosis.

Findings: We observed higher rates of prostate cancer (SIR=1·76, 95 % confidence interval (CI) 1·36–2·24) in Katherine; laryngeal cancer (SIR=2·71, 95 % CI 1·30–4·98), kidney cancer (SIR=1·82, 95 % CI 1·04–2·96) and coronary heart disease (CHD) mortality (SIR=1·81, 95 % CI 1·46–2·33) in Oakey; and lung cancer (SIR=1·83, 95 % CI 1·39–2·38) and CHD mortality (SIR=1·22, 95 % CI 1·01–1·47) in Williamtown. We also saw elevated SIRs for control outcomes. SIRs for all other outcomes and overall cancer were similar across exposure and comparison areas.

Interpretation: There was limited evidence to support an association between living in a PFAS exposure area and risks of cancers or cause-specific deaths.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are man-made chemicals that move through water and land. Their extensive use in household and industrial settings since the 1950s has led to global environmental contamination [1–3]. PFAS are easily absorbed from the environment and distributed and retained in the human body [4,5]. This has led to significant concerns for potential health effects, including cancer.

A particular source of environmental PFAS contamination is aqueous film forming foams (AFFF), used to extinguish liquid fuel fires in aviation settings. In Australia, AFFF products were used on Department of Defence bases for fire emergencies and training purposes, for several decades, starting in the 1970s. This has led to contamination of residential areas surrounding military bases, including Katherine in Northern Territory (NT), Williamtown in New South Wales (NSW) and Oakey in Queensland (Qld) [6–8]. Since the early 2000s, use of these particular foams has been phased out. However, PFAS remain detectable in water sources and land near the military bases [6–8]. The health effects of living in these communities is unknown.

The current epidemiological literature on human cancer in relation to PFAS is largely focussed on perfluorooctanoic acid (PFOA) and involves three types of populations: workers exposed in plants that use or

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produce PFAS (occupational exposure), communities living in areas with documented contamination of the local environment or drinking water supply (community exposure), and the general population (background exposure).

The International Agency for Research on Cancer (IARC) found limited evidence for the carcinogenicity of PFOA and classified PFOA as *possibly carcinogenic to humans* (Group 2B) [9]. Largely based on two studies of community exposure in the mid-Ohio valley region of the USA from the C8 Health Project [10], the IARC considered the evidence for kidney and testicular cancer to be credible while two more recent reviews considered the association for these cancers to be 'suggestive' [11] and 'most likely causal' [12]. All assessments recognised that there were overlaps in cases between the two studies from the C8 Health Project and that estimates for testicular cancer were based on small numbers.

The particular AFFF used in Australia contained perfluorooctane sulfonic acid (PFOS) and perfluorohexane sulfonic acid (PFHxS) as the main active ingredients [13]. The evidence for cancer and cause-specific mortality in populations exposed to PFAS contamination composed of PFOS and PFHxS is sparse. Recently, a Swedish study by Li et al. involving community exposure in such a context reported no evidence for an overall increased risk of cancer [14].

The aim of this study was to examine if incidence of cancers and cause-specific deaths in those who had lived in one of the three PFAS exposure areas in Australia was higher than in comparison areas without known contamination.

2. Methods

2.1. Data sources and study population

The Medicare Enrolment File (MEF) (1983–2019) is a consumer directory for Medicare, Australia's universal healthcare insurance provider. All Australian citizens and permanent residents are eligible to enrol for Medicare. The MEF collects demographic information as well as address history.

The exposed populations were defined as all individuals in the MEF whose recorded address was within any of the three areas of interest affected by PFAS contamination: Katherine (NT), Williamtown (NSW) and Oakey (Qld) as defined by the Australian Department of Defence [15–17]. We extracted all street addresses from the Geocoded National Address File (G-NAF) [18] that fell inside the boundaries of these exposure areas.

The comparison populations were defined as those in the MEF whose recorded address was within any comparison area between 1983 and 2019, and who never had an address in an exposure area. We chose comparison areas (postcodes) on the basis that they had similar socio-demographic profiles to the exposure areas according to the Australian Bureau of Statistics' census data. We chose as many postcodes as necessary to obtain comparison populations that were approximately four times the size of the relevant exposed population. Comparison individuals were sampled from the following postcodes and frequency-matched at a 4:1 ratio to the exposed populations on sex, age, year of first living in an exposure or comparison area, and Aboriginal and Torres Strait Islander status: **for Katherine**: 0800, 0828, 0829, 0835, 0836, 0837, 0838, 0840, 0841, 0845, 0846, 0880, 0886; **for Oakey**: 4311, 4371, 4372, 4373, 4610; and **for Williamtown**: 2334, 2335, 2864, 2865, 2866, 2867, 2477.

Date and site of cancer diagnosis for the study populations were obtained via linkage to the Australian Cancer Database (ACD) (1982–2017) [19]. Date and cause of death were obtained via linkage to the National Death Index (NDI) (1980–2019) [20]. All linkages were performed by the Australian Institute of Health and Welfare via probabilistic methods.

We obtained ethics approval for the study from the nine relevant Australian State and Territory health departments and institutional human research ethics committees: Aboriginal Health and Medical Research Council of NSW Ethics Committee (1545/19), Australian Capital Territory Health Human Research Ethics Committee (2019.STE.00195), Australian Institute of Health and Welfare Ethics Committee (EO2019–3–1048), Australian National University Human Research Ethics Committee (2019/565), NSW Population and Health Services Ethics Committee (2019/ETH12632), NT Department of Health and Menzies School of Health Research Ethics Committee (2019–3472), South Australia Department of Health and Ageing Human Ethics Committee (HREC/19/SAH/62), Tasmanian Health and Medical Human Research Ethics Committee (H0018433) and Western Australian Aboriginal Health Ethics Committee (930).

2.2. Variables

2.2.1. Outcomes

We chose 30 outcomes based on a literature review conducted at an initial phase of the study [21]. This comprised 20 candidate cancers, three composite cancers (any candidate cancer, any other cancer apart from candidate cancers, and any cancer), and four candidate causes of death. Additionally, we examined three causes of death as control outcomes—outcomes not known or thought to be associated with PFAS (Supplementary Table 1).

Incident cancers (diagnosed age $\geq$ 25 years) and deaths (at any age) were ascertained from the ACD and the NDI, respectively, based on International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes, or ICD-9 codes before 1997.

2.2.2. Exposure and other variables

For exposed individuals, we classified person-time from first exposure (earliest recorded date with address in an exposure area) as exposed, even if the individual subsequently moved into a comparison area or elsewhere. We allowed for a lag period (see below) and classified all person-time before first exposure (including if they had lived in a comparison area) and during the lag period as non-exposed. For comparison individuals, we classified all person-time as non-exposed.

Covariates—sex, age and calendar year—were as recorded on the MEF. Aboriginal and Torres Strait Islander status was coded according to the Voluntary Indigenous Identifier (VII) database [22]. Due to unavailability of data before 2002 and under-identification issues, adjustment for Aboriginal and Torres Strait Islander status was performed in sensitivity analysis only.

2.3. Statistical analysis

The time of entry into the cohort was defined as the date of first registration with Medicare. Individuals were followed until they were diagnosed with the specific cancers or died from the specific causes under investigation, or were censored, whichever came first. Individuals were censored at death, after the age of 85, when they moved into an address outside the exposure boundaries (as defined by the Australian Department of Defence) but within the townships of Katherine, Oakey or Williamtown, or until the last available data (i.e., December 2017 for cancers and December 2019 for deaths).

All outcomes were analysed separately by Australian State/Territory of residence at first exposure (or first recorded address in a comparison area). We used indirect standardisation to estimate the standardised incidence ratio (SIR) for each cancer or mortality outcome with Poisson 95 % confidence intervals (CI). In this method, age-sex-calendar period-specific incidence rates in the non-exposed group were applied to the exposed group, to generate an expected number of cases. The SIR is the ratio of total observed to expected cases.

We used a lag period of 10 years as a minimum possible latency period, that is, an expected period between first exposure and onset of disease. Therefore, outcomes occurring during the lag period were attributed to non-exposed person-time. A lag was not applied to individuals who were already living in an exposure area at the start of the

observation period (1983–1984) as they were assumed to have lived there for at least the past 10 years.

In separate sensitivity analysis, we: 1) applied a 10-year lag to the aforementioned individuals; 2) excluded those who were living in an exposure (or comparison) area at the start of the observation period; 3) varied the lag period to 5 or 15 years; 4) adjusted for Aboriginal and Torres Strait Islander status (except in NSW due to low proportions of Aboriginal and Torres Strait Islander residents); and 5) limited the analysis to those who had lived in an exposure area continuously for at least 10 years.

All data analyses and graphs were generated using SAS software (version 9.4).

2.4. Role of funding source

The Australian Government Department of Health funded the Australian National University to independently conduct the study and provided comment on the study protocol and final report. The study team was solely responsible for all outputs.

3. Results

3.1. Description of the study population

We included 318,887 individuals (after exclusion of 5001 individuals with missing or temporally inconsistent dates) from the MEF, of whom 54,343 (17 %) had lived in an exposure area and 264,544 (83 %) had lived in a comparison area between 1983 and 2019. Sample sizes and sociodemographic characteristics by State/Territory and exposure status (ever/never) can be seen in Table 1.

Although NT had the largest number of ever exposed individuals, Qld had the longest total duration of person-time at risk classified as exposed: (378,021 person-years), followed by NT (322,556 person-years) and NSW (115,373 person-years). Altogether, we observed a total of 4·0 million person-years in NT, 3·4 million person-years in Qld and 1·1 million person-years in NSW.

In our study population, 26,721 (8·4 %) people died between 1983 and 2019. Excluding individuals who entered the study after 2017 (n = 3348), 21,611 (6·7 %) had at least one cancer diagnosis, with 24,166 cancers in total diagnosed between 1983 and 2017.

3.2. Cancer outcomes in relation to living in exposure areas

The number of observed and expected cases and SIRs for all outcomes examined are shown in Table 2, and forest plots of SIRs are shown in Figs. 1 and 2. Number of cases, person-years of follow-up and crude rates are in Supplementary Tables 2–4.

In the NT, after adjusting for age, sex and calendar time, the rate of prostate cancer among those who had lived in Katherine was 76 % higher than among those who had lived in the comparison areas (SIR = 1·76, 95 % CI 1·36–2·24). The two composite outcomes (*any candidate cancer* SIR = 1·13, 95 % CI 1·00–1·28; *any cancer* SIR = 1·18, 95 % CI 1·06–1·30), indicated slightly higher rates of cancer among Katherine residents. However, when prostate cancer was removed from the composite measures, there were little or no differences in rates between the exposed and comparison populations (*any candidate cancer excluding prostate* SIR = 1·02, 95 % CI 0·89–1·17; *any cancer excluding prostate* SIR = 1·10, 95 % CI 0·98–1·23). For all other outcomes, interval estimates were compatible with no effect, and we were unable to conclude that rates of these cancers differed between Katherine residents and the

Table 1
Sociodemographic characteristics of study populations, NT, Qld and NSW, 1983–2019.

	NT		Qld		NSW	
Characteristic	Exposed n (%)	Comparison n (%)	Exposed n (%)	Comparison n (%)	Exposed n (%)	Comparison n (%)
Total sample	**25,428**	**130,800**	**21,306**	**102,972**	**7609**	**30,772**
Sex						
Female	13,241 (52)	61,836 (47)	10,862 (51)	51,426 (50)	3776 (50)	15,278 (50)
Male	12,187 (48)	68,964 (53)	10,444 (49)	51,546 (50)	3833 (50)	15,494 (50)
Year first recorded living in exposure or comparison area						
1983–1989	3124 (12)	17,651 (13)	5449 (26)	25,469 (25)	1472 (19)	5977 (19)
1990–1994	3557 (14)	22,980 (18)	2709 (13)	12,892 (13)	1232 (16)	4906 (16)
1995–1999	4519 (18)	17,860 (14)	3096 (15)	11,885 (12)	934 (12)	3836 (12)
2000–2004	3855 (15)	15,066 (12)	2990 (14)	13,413 (13)	1051 (14)	4166 (14)
2005–2009	3537 (14)	19,179 (15)	2465 (12)	13,435 (13)	1312 (17)	5193 (17)
2010–2014	3382 (13)	19,056 (15)	2419 (11)	13,093 (13)	812 (11)	3459 (11)
2015–2019	3454 (14)	19,008 (15)	2178 (10)	12,785 (12)	796 (10)	3235 (11)
Age at first year living in exposure or comparison area						
0–9	8167 (32)	27,234 (21)	6950 (33)	29,959 (29)	1454 (19)	5840 (19)
10–19	3513 (14)	16,556 (13)	3217 (15)	15,965 (16)	1024 (13)	4150 (13)
20–29	5106 (20)	31,341 (24)	4336 (20)	15,666 (15)	1117 (15)	4523 (15)
30–39	4513 (18)	25,239 (19)	2792 (13)	13,796 (13)	888 (12)	3643 (12)
40–49	2292 (9)	15,503 (12)	1636 (8)	10,013 (10)	832 (11)	3395 (11)
50–59	1237 (5)	9317 (7)	1025 (5)	7938 (8)	926 (12)	3697 (12)
60–69	426 (2)	4044 (3)	716 (3)	5455 (5)	832 (11)	3321 (11)
70–79	137 (1)	1207 (1)	411 (2)	2577 (3)	416 (5)	1667 (5)
80–89	37 (0)	322 (0)	183 (1)	1321 (1)	103 (1)	457 (1)
90 +	0[†]	37 (0)	40 (0)	282 (0)	17 (0)	79 (0)
Indigenous status						
No	20,084 (79)	11,7217 (90)	19,584 (92)	99,336 (96)	7386 (97)	29,870 (97)
Yes	5344 (21)	13,583 (10)	1722 (8)	3636 (4)	223 (3)	902 (3)

Table notes

Data sources: Medicare Enrolment File (October 1983–December 2019), Voluntary Indigenous Identifier (VII) database (2002–2019)

1. In this table, exposure was classified at the individual level (rather than at the person-time level). A person was 'exposed' if they ever lived at an address in an exposure area, and 'comparison' if they ever lived in a comparison area and never in an exposure area.
2. Indigenous status was based on those Aboriginal and Torres Strait Islander people who had voluntarily identified in the VII database. The proportions presented have not been weighted for under-identification. These data were extracted on March 2021.
3. Categories were collapsed ([†]) to avoid reporting cell numbers with size ≤ 5.
4. Percentages were rounded to integer values.

Table 2
Observed (O) and expected (E) case numbers in the exposed populations, and standardised incidence ratios (SIR).

	Katherine, NT		Oakey, Qld		Williamtown, NSW	
	O\E cases	SIR (95 % CI)	O\E cases	SIR (95 % CI)	O\E cases	SIR (95 % CI)
Candidate cancer outcomes						
Head and neck	22\20	1·11 (0·69,1·67)	29\30	0·96 (0·65,1·38)	12\11	1·12 (0·58,1·96)
Oesophageal	7\5	1·33 (0·53,2·73)	12\8	1·57 (0·81,2·74)	≤ 5\≤ 5	0·5 (0·1,1·7)
Stomach	≤ 5\≤ 5	1·2 (0·4,2·9)	7\11	0·65 (0·26,1·34)	≤ 5\≤ 5	0·8 (0·2,2·1)
Colorectal	41\36	1·14 (0·82,1·54)	93\81	1·15 (0·93,1·41)	37\41	0·90 (0·63,1·24)
Liver	≤ 5\np	0·5 (0·1,1·2)	≤ 5\np	0·8 (0·3,1·8)	≤ 5\≤ 5	1·2 (0·3,3·0)
Pancreatic	≤ 5\np	0·7 (0·2,1·9)	17\12	1·37 (0·80,2·20)	13\8	1·58 (0·84,2·70)
Laryngeal	≤ 5\≤ 5	0·3 (0·0,1·5)	10\≤ 5	2·71 (1·30,4·98)	≤ 5\≤ 5	1·2 (0·1,4·2)
Lung	30\32	0·94 (0·64,1·34)	61\57	1·07 (0·82,1·37)	57\31	1·83 (1·39,2·38)
Bone	≤ 5\≤ 5	2·1 (0·1,12)	≤ 5\≤ 5	1·4 (0·0,7·6)	No observed events	
Breast	59\52	1·14 (0·87,1·47)	88\99	0·89 (0·71,1·09)	43\45	0·95 (0·69,1·29)
Uterine	9\6	1·56 (0·71,2·95)	18\13	1·38 (0·82,2·19)	7\5	1·30 (0·52,2·67)
Ovarian	≤ 5\≤ 5	1·7 (0·5,3·9)	7\8	0·87 (0·35,1·78)	≤ 5\≤ 5	0·3 (0·0,1·5)
Prostate	66\37	1·76 (1·36,2·24)	107\97	1·10 (0·90,1·33)	49\59	0·83 (0·61,1·09)
Testicular	≤ 5\≤ 5	0·5 (0·1,1·9)	6\6	0·92 (0·34,2·01)	≤ 5\≤ 5	0·6 (0·0,3·6)
Kidney	6\8	0·77 (0·28,1·67)	25\22	1·15 (0·74,1·69)	16\9	1·82 (1·04,2·96)
Bladder	8\≤ 5	2·02 (0·87,3·97)	12\14	0·89 (0·46,1·55)	14\9	1·63 (0·89,2·74)
Thyroid	≤ 5\np	0·7 (0·2,1·5)	22\18	1·20 (0·75,1·82)	6\≤ 5	1·66 (0·61,3·62)
Hodgkin lymphoma	≤ 5\≤ 5	0·5 (0·0,2·8)	≤ 5\≤ 5	0·8 (0·1,2·8)	≤ 5\≤ 5	0·8 (0·0,4·5)
Non-Hodgkin lymphoma	12\11	1·06 (0·55,1·84)	23\24	0·97 (0·61,1·45)	16\13	1·24 (0·71,2·02)
Leukaemia	≤ 5\np	0·4 (0·1,1·2)	23\20	1·12 (0·71,1·69)	10\10	0·96 (0·46,1·76)
Any candidate cancer	270\239	1·13 (1·00,1·28)	521\491	1·06 (0·97,1·16)	263\241	1·09 (0·96,1·23)
Any other cancer	103\80	1·29 (1·05,1·57)	174\192	0·90 (0·78,1·05)	88\89	0·99 (0·79,1·21)
Any cancer	358\305	1·18 (1·06,1·30)	656\653	1·00 (0·93,1·08)	325\310	1·05 (0·94,1·17)
Candidate death outcomes						
Chronic kidney disease	8\8	0·94 (0·41,1·86)	10\10	1·00 (0·48,1·83)	7\5	1·29 (0·52,2·65)
Coronary heart disease	40\37	1·07 (0·77,1·46)	114\93	1·22 (1·01,1·47)	92\51	1·81 (1·46,2·23)
Stroke	12\10	1·22 (0·63,2·13)	27\29	0·92 (0·60,1·33)	29\21	1·37 (0·92,1·97)
Liver disease	8\17	0·46 (0·20,0·91)	15\14	1·10 (0·62,1·82)	6\≤ 5	1·25 (0·46,2·71)
Control death outcomes						
Infectious or parasitic	8\9	0·93 (0·40,1·82)	10\8	1·31 (0·63,2·41)	10\6	1·67 (0·80,3·07)
All external causes apart from self-harm	35\51	0·69 (0·48,0·96)	72\52	1·38 (1·08,1·73)	17\17	1·01 (0·59,1·62)
Intentional self-harm	30\31	0·98 (0·66,1·40)	53\37	1·44 (1·08,1·89)	14\7	1·89 (1·04,3·18)

Table notes
1. The standardised incidence ratio (SIR) is the ratio of the number of observed cancer cases/deaths in the exposed population to the number that would be observed ('expected') if the exposed population experienced the same cancer/death rates as the comparison population.
2. In this table, exposure was classified at the person-time level. In individuals who were 'ever exposed', we classified person-time from first exposure as exposed even if the individual subsequently moved into a comparison area or elsewhere. We allowed for a lag period, and classified all person-time before first exposure and during the lag period as non-exposed. In comparison individuals, we classified all person-time as non-exposed.
3. SIRs were adjusted for age, sex and calendar period. For death outcomes, the first age band was 15 years (0–15 years), and 5 years thereafter. For cancer outcomes, 5-year age bands were used from 25 years. The final age band for all outcomes was 70–85 years. A 10-year lag period was applied, therefore the first calendar period band was 15 years (1983–1998), and 5 years thereafter. SIRs are represented in forest plots in Figs 1 and 2.
4. Number of cases, person-years of follow-up and crude rates are in Supplementary Tables 2-4.
5. Cells have been suppressed to avoid reporting cell numbers with size ≤ 5 (np: not provided). SIRs were rounded to two significant figures where the number of observed cases was ≤ 5.
6. Expected cases were rounded to integer values.

comparison population.

In Qld, the adjusted rate of laryngeal cancer in Oakey residents was 2·7-fold the rate among those who had lived in the comparison areas (SIR = 2·71, 95 % CI 1·30–4·98). However, this estimate was imprecise due to a small number of cases. For the other candidate outcomes in Oakey, effect sizes (in both directions) were not large and interval estimates were compatible with no effect. Composite measurements suggested little or no differences between Oakey residents and the comparison population (*any candidate cancer* SIR = 1·06, 95 % CI 0·97–1·16; *any cancer* SIR = 1·00, 95 % CI 0·93–1·08).

In NSW, the adjusted rates of kidney and lung cancers in those who had lived in Williamtown were around 80 % higher than the rates in those who had lived in the comparison areas (*kidney cancer* SIR = 1·82, 95 % CI 1·04–2·96; *lung cancer* SIR = 1·83, 95 % CI 1·39–2·38). For the other candidate outcomes, the precision of the estimates varied but all were compatible with no effect. Composite measurements suggested small or no differences between Williamtown residents and the comparison population (*any candidate cancer* SIR = 1·09, 95 % CI 0·96–1·23; *any cancer* SIR = 1·05, 95 % CI 0·94–1·17).

3.3. Mortality outcomes in relation to living in exposure areas

In the NT, after adjusting for age, sex and calendar time, the rate of death from liver disease was 54 % lower in those who had lived in Katherine compared to those who had lived in comparison areas (SIR = 0·46, 95 % CI 0·20–0·91). The rate of death from external causes apart from self-harm was also 31 % lower in Katherine (SIR = 0·69, 95 % CI 0·48–0·96). For the other candidate and control outcomes, effect sizes were generally small and imprecise and compatible with no effect.

In Qld, after age, sex and calendar time adjustments, the rate of death from coronary heart disease (CHD) was 22 % higher in those who had lived in Oakey compared to those who had lived in comparison areas (SIR = 1·22, 95 % CI 1·01–1·47). For the other candidate outcomes, estimates were too imprecise to make any conclusions about the size or direction of effects. For two of three control outcomes examined, we estimated around 40 % higher death rates associated with having lived in Oakey (*external causes apart from self-harm* SIR = 1·38, 95 % CI 1·08–1·73; *intentional self-harm* SIR = 1·44, 95 % CI 1·08–1·89).

In NSW, the adjusted rate of death from CHD was 81 % higher in Williamtown residents compared to residents of comparison areas (SIR

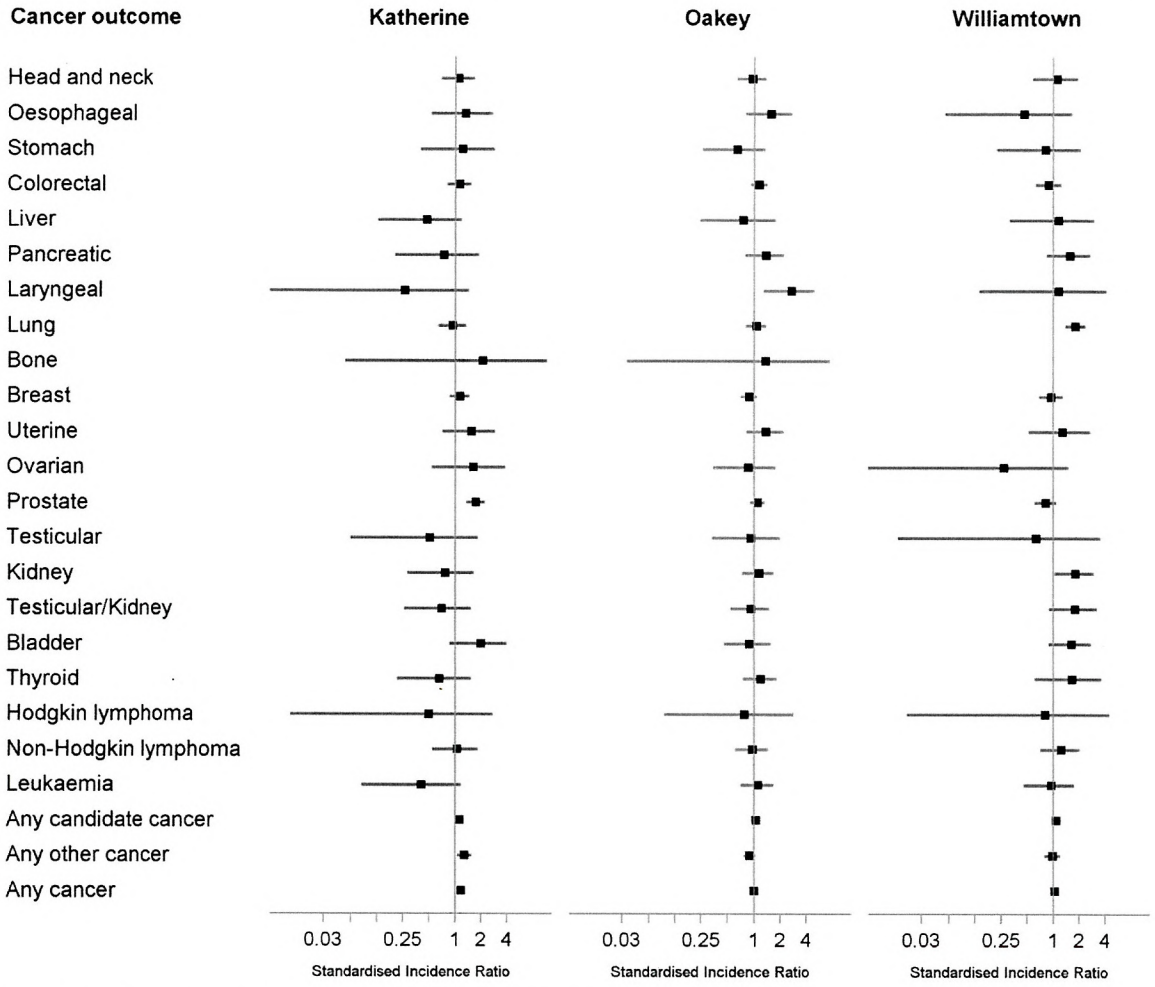

Fig. 1. Forest plot showing standardised incidence ratios (SIR) for cancer outcomes.
Figure notes
Data sources: Medicare Enrolment File (October 1983–December 2019) linked to Australian Cancer Database (up to December 2017).
1. Forest plot shows point estimates of SIRs (filled squares) and associated 95 % confidence intervals (horizontal lines), and solid vertical line of no effect. SIRs were adjusted for age, sex and calendar period.
2. See Table 2 for numbers of observed and expected cases, and SIRs.
3. SIRs are on a log scale.

= 1·81, 95 % CI 1·46–2·23). We also observed a higher death rate from intentional self-harm in Williamtown (SIR = 1·89, 95 % CI 1·04–3·18). For the remaining candidate and control causes of death studied, while all SIR point estimates were above 1, interval estimates were too wide to make any determinations about effect sizes or direction, thus we cannot conclude that rates of these outcomes differed between Williamtown residents and the comparison population.

Sensitivity analyses largely did not change our conclusions (Supplementary Tables 5–10); however, we note that in Williamtown the SIR for bladder cancer was elevated when we limited the exposed group to those who had lived in the exposure areas for 10 years (Supplementary Table 5) and for pancreatic cancer when a lag period of 5 years instead of 10 years was applied (Supplementary Table 7).

4. Discussion

Overall rates of cancers were very similar in the exposed populations of Katherine, Oakey and Williamtown and their respective comparison populations, but we found higher-than-expected rates of prostate cancer in Katherine, laryngeal cancer in Oakey and kidney and lung cancers in Williamtown. We estimated a lower rate of death from liver disease in Katherine, higher rates of death from coronary heart disease in Oakey and Williamtown, and higher rates of death from control outcomes in Oakey and Williamtown.

The largest relative effect estimated was the 2·7-fold rate of laryngeal cancer in Oakey. The current evidence on the link between PFAS and laryngeal cancer is sparse. One occupational mortality study, [23] and another by Li et al. [14] examining incidence in a community with PFAS exposure similar to that in our study (primarily PFOS and PFHxS) did not report associations with laryngeal cancer. However, both studies had very few cases [14,23]. We were similarly limited by small numbers of cases in Katherine and Williamtown, and our estimate for Oakey had a wide confidence interval (1·30–4·98).

We were able to estimate SIRs for prostate cancer with more precision, with results showing a higher-than-expected rate in Katherine, but not in Oakey or Williamtown. Previous evidence for a link to prostate cancer is low. Studies in those with occupational, community and background exposure have largely not reported associations with prostate cancer [24–29]; Li et al. reported a decreased risk for prostate cancer but noted this was inconsistent with current evidence [14].

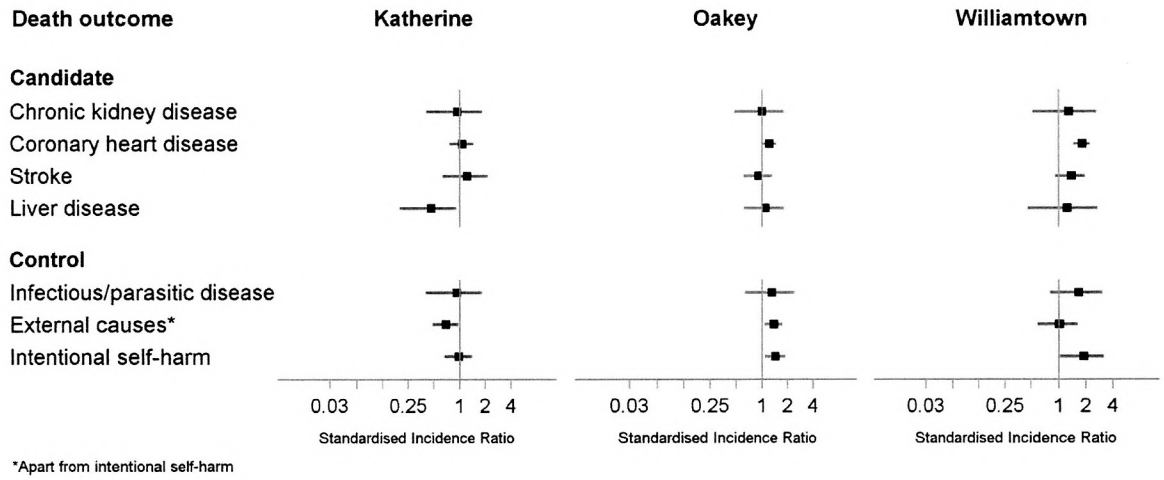

Fig. 2. Forest plot showing standardised incidence ratios (SIR) for cause-specific mortality outcomes.
Figure notes
Data sources: Medicare Enrolment File (October 1983–December 2019) linked to National Death Index (up to December 2019).
1. Forest plot shows point estimates of SIRs (filled squares) and associated 95 % confidence intervals (horizontal lines), and solid vertical line of no effect. SIRs were adjusted for age, sex and calendar period.
2. See Table 2 for numbers of observed and expected cases, and SIRs.
3. SIRs are on a log scale.

The findings for kidney cancer, where we found elevated rates in Williamtown but not in Oakey or Katherine, are of particular interest as there is some prior evidence for an association to PFOA specifically. Three studies of two cohorts with community exposure [27,28,30] and a case-control study at background levels [31] reported associations between PFOA and increased incidence of kidney cancer. At occupational (i.e. higher) exposures, one of two studies reported a link to kidney cancer mortality [25,32]. A recent study provided additional evidence for a link where exposure composition was dominated by PFOS and PFHxS [14]. Animal studies have found that PFOA exposure can promote liver, pancreatic and testicular adenomas [33,34] but not tumours of the kidney [35]. The relevance of this animal research to humans is unclear [35]. Our finding on kidney cancer, while not consistent across exposure areas, merits further study given similar observations in other PFAS-contaminated areas internationally.

While previous evidence is also suggestive of a link between PFAS exposure and testicular cancer, low numbers meant that we had limited statistical power to detect an effect in any exposure area.

Our finding of elevated lung cancer incidence in Williamtown is not supported by other evidence. As far as we are aware, there is no prior evidence for a relationship between PFAS exposure and lung cancer incidence or mortality [23,27,28,32,36–38], therefore our results should be viewed with caution, particularly as we did not have information on tobacco use.

We saw higher rates of pancreatic and bladder cancers in Williamtown in separate sensitivity analyses. There is little to no prior support for a relationship between PFAS exposure and increased pancreatic or bladder cancer incidence or mortality [23,25,27,28,32,36,38–41] although mortality studies for these cancers have generally had very few cases. These results should be viewed cautiously, especially given the large number of analyses conducted and potential for significant findings occurring by chance alone.

Regarding mortality outcomes, we estimated higher rates of death from CHD in both Oakey and Williamtown. Occupational exposure studies have not reported increased deaths from CHD or ischaemic heart disease [25,32,36,42]. Studies examining prevalence/incidence at various exposure levels have not found a link across a variety of endpoints, including ischaemic heart disease, coronary artery disease, angina and/or heart attack [24,25,42,43–45], apart from one study [46]. Studies in laboratory rodents have not reported any histological or morphological alterations in the heart [35]. There is, however, some evidence for a relationship between PFAS and biomarkers of cardiovascular health in humans including elevated levels of total cholesterol, LDL and triglycerides [4,47,48].

Given that outcomes were chosen *a priori* informed by existing evidence, we interpreted results in the context of previous findings and did not perform a statistical correction for multiple comparisons. However, the possibility of any individual finding arising by chance must be kept in mind, particularly as multiple tests of association were conducted.

A strength of our study is the unbiased selection of everyone who ever lived in the exposure areas over the 35 years from 1983 to 2019. However, we did not capture those who were exposed prior to the inception of the MEF (PFAS exposure in Australia is possible as early as the 1970s). Individuals who were exposed earlier may have developed cancer or died before they could be observed in this study, leading to underestimation of rates. However, PFAS exposure in Katherine, Oakey and Williamtown is thought to have peaked in the 2000s, thus potentially minimising the impact of left-truncation of the cohort. Additionally, residence in an exposure area may not correlate with bodily absorption of PFAS.

Using national cancer and death registries, we had complete follow-up of cases even if subjects moved away to a different state. However, we were still limited by small numbers for many rare cancers, or in the case of outcomes with long latency periods, insufficient follow-up time. We lacked information on individual socioeconomic status and behavioural and biological factors. While we chose comparison areas that were similar to each exposure area on socioeconomic indices, we did not have individual socioeconomic status to assess the comparability between the exposed and comparison populations. Furthermore, any dissimilarity may have increased over the long study period due to social mobility. We had indirect evidence of the probable unequal distribution of risk factors across the populations, seen in the elevated control death outcomes in both Oakey and Williamtown, and for non-candidate cancers in Katherine. Apart from age and sex, we could not account for other risk factors such as alcohol intake, smoking, obesity and occupational exposure to PFAS.

In the current study, we did not measure or attempt historical reconstructions of serum PFAS concentrations. However, cross-sectional

measurements from 2016 to 2019 provide some context for the levels of exposure: the median blood PFAS levels across the three exposure areas (n = 2710) ranged from: 4·8–6·1 ng/ml for PFOS, 2·9–3·9 ng/ml for PFHxS and 1·3–1·9 ng/ml for PFOA [49], bearing in mind that measurement at one point in time may not reflect cumulative exposure or changes over time (in comparison, the median blood PFAS levels in Ronneby, Sweden were: 245 ng/ml for PFOS, 277 ng/ml for PFHxS and 18 ng/ml for PFOA [22]). On the strong assumption that exposure levels and PFAS composition were similar over the study period, we would expect reasonably consistent findings on these outcomes across the three areas, at least in the direction of effect. This was not the case.

5. Conclusion

Our study found no overall increased risk of cancer, and limited evidence for increased risk of any specific cancer or cause-specific death in three Australian communities with PFAS exposure from firefighting foams.

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Australian Government Department of Health.

Link to study protocol

https://rsph.anu.edu.au/files/PFAS%20Health%20Study%20Dat%20Linkage%20Study%20Research%20Protocol%20v1.0_Web_accessible%20for%20website_0.pdf#overlay-context=research/projects/pfas-health-study.

Data sharing

The data used in this study are not available to individuals other than nominated members of the study team under the Australian Government Department of Health Data Custodian requirements for data linked to the Medicare Enrolment File.

CRediT authorship contribution statement

RK and MK conceived the study; HDL, RK, BA, CD and MK contributed to study design; HDL did the analytical calculations; HDL, RH and KS did the literature search. HDL wrote the first draft of the manuscript and all authors provided critical feedback and approved the final manuscript.

Declaration of interests

MDK worked part-time for the Australian Government Department of Health between 2020 and 2022 on national COVID-19 response. The other authors declare that they have no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2022.102296.

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